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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/578,900
Filing Date: May 26, 2000
Appellant(s): CARULLI ET AL.

Christopher L. North
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 14, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. However, the Examiner would like to further clarify the issues.

First, it is respectfully pointed out that there is not only a single issue remaining, but rather two issues which should be considered together as well as separately. Specifically, issue number one is whether the claimed methods of identifying molecules involved in lipid regulation have utility as required under 35 U.S.C. § 101. Issue number two is whether the claimed methods of identifying molecules involved in lipid regulation are enabled under 35 U.S.C. § 112, first paragraph. The rejection of record indicates the reasons why the claimed methods do not have a substantial utility. Since the claimed methods do not have a substantial utility, one of skill in the art would not know how to make and use the claimed methods without first performing additional experimentation. Therefore, since the claimed method does not have a substantial utility, the claimed methods are also not enabled because one of skill in the art would not be able to make and use a method that does not have a substantial utility. The utility and enablement issues should be considered together when the claimed methods do not have a substantial utility. However, one of skill in the art would not be able to make and use the claimed methods without first performing an undue amount of additional experimentation regardless if the claimed methods have a substantial utility or not. As such, the issues regarding utility and enablement should be considered together and separate. If the claimed methods do not have a substantial utility then the claimed methods are also not enabled. However, any finding that the claimed methods have a substantial utility should not, in and of itself, obviate the enablement rejection, and the issues of enablement should be considered separate from the enablement rejection.

The instant claims are drawn to method of identifying molecules that are involved in lipid regulation by identifying molecules that bind to HBM and/or Zmax1 as well as identifying

molecules that bind to the nucleic acids encoding HBM and/or Zax1. It is respectfully pointed out that the claims are NOT drawn to HBM and/or Zmax1 themselves (or the nucleic acids encoding HBM and Zmax1), rather the claims are drawn to methods of identifying molecules that are involved in lipid regulation using Zmax1 and/or HBM. Therefore, when considering the utility of the instant claims, the issue is not merely whether Zmax1 and HBM have utility in and of themselves, but whether the claimed methods of identifying molecules involved in lipid regulation using HBM and Zmax1 have utility under 35 U.S.C. § 101. It is acknowledged that a claim only needs to have one substantial utility. However, the instant claims are explicitly drawn to methods of identifying molecules that are involved in lipid regulation. Therefore, it is the methods that must have a substantial utility, not just the genes used to identify the molecules. To be clear, it is not sufficient to simply show that HBM and Zmax1 themselves have a substantial utility, rather HBM and Zmax1 must actually be involved in lipid regulation in order for the instant methods to have a substantial utility.

Although HBM and Zmax1 have specific, credible and substantial asserted utility in and of themselves because they have been associated with particular lipid profiles, the claimed methods do not have a substantial utility because neither HBM nor Zmax1 has been shown to be directly involved in lipid regulation. The evidence presented has only established that there is an association between lipid regulation and the HBM/Zmax1 genes, the evidence provided by appellant does not established that the association is causative. Without such knowledge the claimed methods can not be used to identify molecules involved in lipid regulation. Thus, the claimed methods are not enabled because an undue amount of additional experimentation would

be required in order for one of skill in the art to be able to make and use the claimed methods to identify molecules that are involved in lipid regulation.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 2, 6, 7, and 48-61 stand or fall together, which is correct.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ye, S.Q. et al. "Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol" American Journal of Clinical Nutrition, vol72(suppl), November 2000, pp. 1275S-1284S.

Willnow, T.E. et al. "Lipoprotein receptors: new roles for ancient proteins" Nature Cell Biology, vol1, October 1999, pp. E157-E162.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 2, 6, 7 and 48-61 stand finally rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility for the reasons of record, which are reiterated below for convenience.

Claims 1, 2, 6, 7 and 42-61 stand finally rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility, one skilled in the art would not know how to make and use the claimed invention.

The instant claims are drawn to a method for identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to, or that inhibit the binding of a molecule to, High Bone Mass (HBM) protein or Zmax1 protein (e.g., see claim 1, 53); as well as a method for identification of candidate molecules involved in lipid regulation by identifying molecules that bind to a nucleic acid encoding Zmax1 or HBM (e.g., see claim 6).

The specification discloses that the nucleic acid sequence encoding the High Bone Mass (HBM) protein is an allelic variant of the nucleic acid encoding Zmax1. That is, the nucleic acids encoding HBM and Zmax1 have highly similar sequences. The specification further discloses that the protein encoded by the HBM gene is associated with elevated bone mass while the protein encoded by Zmax1 gene is not associated with aberrant bone mass (spec. page 18, line

19-24). The specification further discloses that the Zmax1 nucleic acid sequence is common in the human population, while the HBM sequence is rare (spec. page 19 line 3-8). The pedigree of the individuals is used in genetic linkage analysis and it is concluded that HBM is an inheritable trait (spec. page 22, line 16 through page 23, line 5; and Example 1).

The specification discloses that Zmax1 is related to the low density lipoprotein receptor (LDL receptor) (see spec. page 83, line 13-25; and p. 125). However, the relationship of Zmax1 to the LDL receptor appears to be based purely sequence homology and the level of homology (sequence similarity) between Zmax1 and the LDL receptor is not disclosed. Furthermore, the specification as filed does not disclose evidence indicating that Zmax1 or any polymorphism thereof (including HBM) are genes that are directly involved in or are a causative agent of lipid regulation—i.e., the specification as filed has not established that either HBM or Zmax1 has a direct function in lipid regulation. It is noted that in order for the claimed methods to have substantial utility it is critical that all of the elements of the claimed method are directly involved in lipid regulation.

Regarding the involvement of HBM in lipid regulation, the specification discloses that biochemical tests were performed to measure the serum levels of various lipid containing molecules and precursors in affected and unaffected HBM family members to test whether HBM affects lipid regulation (see Example 3, starting at p. 125). The specification discloses that triglycerides and VLDL were "generally lower in affected [i.e. HBM+] than unaffected [i.e. HBM-] individuals", while HDL and the ratio of LDL to HDL was "generally higher in affected males than unaffected males" (see p. 126, line 21-27). It is respectfully pointed out that this data

merely indicates an association between HBM and lipid levels, and is not indicative that HBM has a direct function in regulating lipid levels.

Regarding the involvement of Zmax1 and lipid regulation, it is acknowledged that the specification asserts that 1) Zmax1 has sequence similarity to the LDL family of receptors, and 2) Zmax1 binds to "several" proteins, one of which is ApoE. It is noted that the specification does not indicate the specific similarity of Zamx1 and the LDL receptors, or what other proteins bind to Zmax1. Furthermore, there is no indication of the conditions in which ApoE binds to Zmax1, therefore it is unclear if ApoE binding specifically binds Zmax1. Additionally, any proteins that bind to Zmax1 that are not involved in lipid regulation would indicate that Zmax1 is involved in functions other than lipid regulation.

Therefore, the only links between Zmax1 and lipid regulation disclosed in the original specification are 1) sequence homology between Zmax1 and LDL-receptor, and 2) ApoE is one of "several" undisclosed proteins that bind to Zmax1. The only link between HBM and lipid regulation is the indication that persons with the HBM polymorphism show a generally lower serum level of triglycerides and VLDL and a generally higher serum level of HDL, compared to controls.

Serum lipid regulation is recognized in the art as a very complex process that involves not one single factor, but many different factors including diet as well as the function of many different genes. For instance, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, Ye reviews a number of DNA sequence polymorphisms (specifically, polymorphisms in the genes encoding ApoA-I, ApoA-IV, ApoB, ApoC-III, ApoE,

LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasma lipid regulation. Regarding the effects of these sequence polymorphisms on serum lipid levels, Ye teaches that the effects of the polymorphisms on lipid metabolism have been inconsistent due to a number of factors. Specifically, Ye teaches,

> "Although more and more data are available on the effects of genetic polymorphisms in genes related to lipid metabolism and the responsiveness to dietary fat and cholesterol, no consistent effects of most reported genetic factors have been seen. The major problems related to these discrepancies are sample size, effects of age and sex, different ethnic and cultural (dietary) backgrounds of the participants, different dietary protocols used, and the difficulty of insuring compliance. More clinical trials in large populations with standardized protocols are needed to study further the effects of these polymorphisms on the responsiveness to dietary fat and cholesterol." (see p. 1282S, first column, emphasis added).

Furthermore, the relevant art at the time of filing recognized that LDL-receptors could be involved in functions other than lipid regulation. For instance, Willnow et al. (Nature Cell Biol.; Vol. 1, October 1999, pages E157-E162) teaches,

> "Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and membrane synthesis. This perception has now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and entirely unexpected new role as transducers of extracellular signals." (See abstract, emphasis added).

Therefore, the prior art teaches that LDL-receptors (which appellants assert includes Zmax1) can be involved in processes other than lipid regulation, such as endocytic uptake of retinoids and steroids. As such, additional experimentation would be required in order for one of skill in the art to determine if an LDL-receptor family member (such as Zmax1) is actually involved in lipid regulation.

The claimed methods of identifying molecules that are involved in lipid regulation do not have a substantial asserted utility because the specification fails to disclose the direct involvement of either HBM or Zmax1 in lipid regulation. The art at the time of filing clearly indicates that lipid regulation is a complex process that involves a number of different factors including diet, as well as a number of different genes. Furthermore, the art at the time of filing clearly indicates that LDL-receptor family members can have functions other than lipid regulation. Therefore, the asserted use for the claimed methods is not supported by either a substantial or well-established utility. The only immediately apparent utility for HBM and Zmax1 would be for the further scientific characterization of their possible involvement in the lipid regulation, bone development, osteoporosis, etc. Since the specification does not specifically show that HBM and/or Zmax1 are directly involved in lipid regulation (i.e., the function of HBM and Zmax1 has not been disclosed), it is unclear how one of skill in the art would use HBM or Zmax1 in a method to identify molecules or candidate molecules involved in lipid regulation without performing additional experimentation to first establish that HBM and/or Zmax1 are directly involved in lipid regulation.

Should HBM and Zmax1 have credible specific and substantial utility themselves without a clear indication of their functions, one of skill in the art would still have to perform additionally experimentation in order to be able to make and use HBM or Zmax1 in the claimed methods of identifying molecules that are involved in lipid regulation. The amount of additional experimentation required is deemed to be undue in view of teachings in the prior art that 1) lipid regulation is a complex multi-factorial process that involves many different elements, and 2) LDL-receptors (which may include Zmax1) can be involved in processes other than lipid

regulation. The quantity of experimentation required to practice the invention as claimed would require the elucidation of the actual function of HBM and/or Zmax1 and would include characterization of the coding sequences, protein sequences, protein function, ability of the protein to regulate lipid levels, etc.

(11) Response to Argument

The appellants argue that the rejections should be reversed because the Office has failed to meet the initial burden of challenging a presumptively correct assertion of utility in the disclosure (see p. 5, second paragraph of the brief). The appellants assert that the Examiner has failed to give proper credit to the direct biological evidence that the claimed methods have a credible, specific and substantial utility which is allegedly presented in the Specification and which is allegedly supported by additional circumstantial evidence described in the specification and independent biological evidence.

In reply, it is acknowledged that the Examiner must accept a utility asserted by the appellants unless the Examiner has evidence or sound scientific reasoning to rebut the assertion. *See, In re Oetiker,* 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). It is noted that the instant claims are drawn to methods of identifying molecules that are involved in lipid regulation by identifying molecules that bind to, or inhibit binding of a molecule to, HBM or Zmax1 (e.g., see claim 1, 53); as well as by identifying molecules that bind to a nucleic acid encoding Zmax1 or HBM (e.g., see claim 6). It is respectfully pointed out that in order for the claims to have utility the methods must have utility for identifying molecules involved in lipid regulation, as indicated in the preamble of the claims. As such, it is essential that the method steps set forth in the claims actually identify molecules that are involved in lipid regulation. Since the method steps include

identifying molecules that merely bind to Zmax1 and/or HBM as well as identifying molecules that merely bind to the nucleic acid sequences encoding Zmax1 and/or HBM it is imperative that Zmax1 and HBM must be involved in lipid regulation in order for the claimed methods to have a real world utility. To be clear, it is not sufficient to merely associate Zmax1 and HBM with lipid levels, but substantial evidence must be present in the original specification to indicate that Zmax1 and HBM have direct lipid regulating functions, which the specification does not teach.

In the instant case, it is acknowledged that the specification indicates that the presence of HBM is correlated to high bone mass as well as lower VLDL levels and higher HDL levels. That is, individuals who have been identified as having the HBM gene, have been shown to have a generally higher bone mass as well as lower VLDL levels and higher HDL levels. However, individuals having the Zmax1 gene (an alternative variation of the HBM gene) do not show aberrant bone mass or lipid levels. In analyzing this evidence, it is pointed out that the evidence only indicates a mere association between HBM and high bone mass, low VLDL and high HDL levels. This does not indicate that either HBM or Zmax1 is directly involved in regulating lipid levels.

It is also acknowledged that the specification discloses that Zmax1 is highly homologous to LDL receptor, and that ApoE is one of "several" proteins that bind to Zmax1. In analyzing this evidence, it is important to determine if all LDL receptors are solely involved in lipid regulation or if they can be involved in other functions that are not associated with lipid regulation. Looking to the prior art to determine the state of the art at the time of filing, it is clear that LDL-receptors can be involved in non-lipid regulating functions, such as the cellular uptake of retinoids and steroids via endocytosis (e.g., see Willnow, abstract, as indicated above).

Furthermore, the prior art with respect to lipid metabolism indicates that lipid regulation is a complex multi-factorial process that involves many different factors including diet, as well as specific genes (e.g., see Ye, as indicated above). Specifically, Ye teaches, "Although more and more data are available on the effects of genetic polymorphisms in genes related to lipid metabolism and the responsiveness to dietary fat and cholesterol, no consistent effects of most reported genetic factors have been seen." (See Ye, p. 1282S, first column; emphasis added). Additionally, the fact that that "several proteins" bind to Zmax1, is indicative that further experimentation is needed in order to determine which proteins specifically bind to Zmax1 and to determine the specific function of Zmax1 with respect to the binding of each protein.

The teachings of Willnow and Ye as well as the analysis set forth above, rebut appellants assertion that HBM and Zmax1 are directly involved in lipid regulation, and the Examiner has not misapplied the standard set forth by the courts and interpreted by the Office in the *Utility Examination Guidelines.*

The appellants assert that the instant claims have specific and substantial utility because the asserted utility is directly and specifically related to the function of HBM and Zmax1 in mediating lipid regulation as described in the specification (see p. 6 of the Brief). The appellants also assert that the Office has not alleged that the identification of a molecule involved in lipid regulation is not a specific and substantial utility (see p. 6 of the Brief).

To be clear, a method of identifying molecule involved in lipid regulation would have specific and substantial utility if all of the elements of said method were shown to be involved in lipid regulation. In the instant case, the claims are drawn to methods of identifying molecules

that are involved in lipid regulation by identifying molecules that bind to, or inhibit binding of a molecule to, HBM or Zmax1 (e.g., see claim 1, 53), as well as by identifying molecules that bind to a nucleic acid encoding Zmax1 or HBM (e.g., see claim 6). Here, it is imperative that Zmax1 and HBM must be involved in lipid regulation in order for the claimed methods to have a real world utility. However, since the function of Zmax1 and HBM has not been determined, additional experimentation would be required in order to determine if Zmax1 and HBM were directly involved in lipid regulation for the claimed methods to have a real world utility.

It is acknowledged that the HBM and Zmax1 genes have utility in and of themselves, based on the disclosure that they are associated with particular lipid profiles. However, the instant invention limited to either the HBM or Zmax1 gene. The instant invention is a method of identifying molecules that are involved in lipid regulation. Since the HBM and Zmax1 genes have not been shown to be causative to any extent with respect to lipid regulation, the claimed method of identifying molecules that are involved in lipid regulation does not have substantial utility.

The appellants assert that the credibility of the asserted utility is supported by experimental data. Specifically, appellants contend that the data disclosed in the specification "clearly establish that the HBM polymorphism of Zmax1 is associated with an altered lipid profile in addition to its role in bone mass modulation." (See p. 7, last paragraph of the Brief). It is acknowledged that the disclosed data establish that HBM is **associated** with altered lipid levels. However, as previously indicated, the mere association of HBM with altered lipid levels does not indicate that HBM is directly involved in regulating lipid levels. That is, the data does not indicate that the presence of HBM causes the altered lipid levels, only that the presence of

the HBM polymorphism is associated with altered lipid levels. Since the data disclosed does not establish that HBM and/or Zmax1 is directly involved in lipid regulation, appellants have not established that the claimed methods have a real world utility and could be used to identify molecules involved in lipid regulation.

The appellants also contend that the data disclosed in the specification is consistent with the knowledge in the art at the time the application was filed. Specifically, appellants contend that Zmax1 has been disclosed as having a high degree of sequence homology and features in common with the LDL receptor (see p. 8 of the Brief).

In response, it is acknowledged that the specification has asserted high sequence homology between Zmax1 and the LDL receptor, thus indicating that Zmax1 is a member of the LDL receptor family. When considering if sequence homology to the LDL receptor is sufficient to indicate that Zmax1 is directly involved in lipid regulation, one must consider the function of known LDL receptor family members. The prior art indicates that at least one LDL-receptor family member (Megalin) is not involved in lipid regulation, but is involved in the cellular uptake of retinoids and steroids (e.g., see Willnow, as indicated above). Therefore, the observation that Zmax1 has a high level of sequence homology to the LDL receptor is not sufficient to indicate that Zmax1 is directly involved in lipid regulation.

Appellants also argue that that the specification discloses that Zmax1 binds to several proteins including apolipoprotein E (ApoE). It is acknowledged that the specification does disclose that "several" proteins bind to Zmax1, including ApoE, which is involved in lipid regulation (e.g., see p. 115, line 11 of the specification). The specification does not disclose the

protocols that were used to determine that ApoE binds to Zmax1, nor are the other proteins which bind to Zmax1 been disclosed. As such, additional experimentation would be required in order to determine if the binding of ApoE to Zmax1 and had any biological effect. Since ApoE is only one of several proteins which have been found to bind Zmax1 (see p. 115, line 11 of the specification) additional experimentation would be required to identify which proteins that bind to Zmax1 result in a biological effect. It is possible that the other proteins which have been found to bid Zmax1, but which have not been disclosed, may have functions that are not involved in lipid regulation. The appellants also refer to a prior art abstract (Zabaglia et al., cited in prior art section as relied upon by appellants) as further circumstantial evidence that allegedly adds to the credibility of the asserted utility. It is asserted that Zabaglia shows a correlation between lipid profile parameters and bone mineral density. It is respectfully pointed out that Zabaglia's own conclusion states, "The conclusions were that the lipid profile variables did not show a significant association with bone mass and could not be used as indicators for bone mineral density." (See the last line of the abstract of Zabaglia). Appellants assert that this does not contradict the data disclosed in the present application. The Examiner respectfully disagrees with the appellants. Zabaglia conducted independent research in order to determine if a correlation between lipid levels and bone density could be found and concluded that lipid profiles cannot accurately be used to determine bone density. Zabaglia's conclusion speaks for itself.

The appellants also refer to a number of post filing journal articles as support for their assertion of a correlation between lipid levels and bone density (e.g., Parhami et al., 2001; Fujino

et al., 2003; Magoori et al., 2002; all of which are cited in the prior art section relied upon by the appellants). The appellants contend that Parhami cites prior art references and thus should be considered as a description of the prior art. It is pointed out that none of the prior art references cited by Parhami have been submitted for consideration. Furthermore, Parhami merely indicates that there is evidence of a link between osteoporosis and cardiovascular disease. Evidence of a link between osteoporosis and cardiovascular disease does not establish that Zmax1 or HBM are directly involved in lipid regulation. Additionally, Fujino and Magoori are articles that were published after the filing of the instant application. The evidence presented in the specification as filed or the cited prior art does not establish that Zmax1 or HBM are directly involved in lipid regulation.

With respect to the teaching of Ye, appellants contend that Ye does not in any way cast doubt on whether those polymorphisms or the HBM polymorphism appear in genes related to lipid regulation and does not provide a reason to doubt the utility of the present invention. In reply, as previously indicated, Ye teaches that lipid regulation is a complex multi-factorial process that involves a number of different factors including diet as well as genetics, and specifically indicates a number of different genes and polymorphisms that are involved in lipid regulation. Ye is pertinent to the instant case because Ye establishes that many different factors can be involved in lipid regulation. In view of the complex nature of lipid regulation, as taught by Ye, it is clear that a mere observation that a gene or polymorphism (such as HBM or Zmax1) is associated with a particular lipid level does not establish that the gene or polymorphism is directly involved in lipid regulation. The observation that a gene or polymorphism is associated

with a particular lipid profile would require additional experimentation to establish that the gene or polymorphism is actually directly involved in lipid regulation, let alone be useful in a method to identify molecules involved in lipid regulation.

With respect to the teachings of Willnow, appellants contend that the asserted utility is supported by, but does not rest on, familial association of Zmax1 and HBM to the LDL receptor. The appellants also contend that Willnow does not contest the biological data disclosed in the specification which also supports the asserted utility, and that Willnow does not provide a reason to doubt the credibility of the asserted utility.

In reply, Willnow teaches that LDL receptors are a family of receptors that can have diverse functions including lipid regulation, as well as non-lipid regulating functions. Willnow specifically teaches a receptor that has high homology to the LDL receptor, Megalin (see Willnow et al.), which is involved in the cellular uptake of retinoids and steroids. Therefore, Willnow teaches that the fact that a protein is a member of the LDL receptor family of proteins does not establish that the protein is directly involved in lipid regulation. As such, Willnow directly rebuts the assertion that Zmax1 and HBM are directly involved in lipid regulation base on the fact that they are highly homologous to the LDL receptor and may be members of the LDL receptor family

of proteins. It is acknowledged that Willnow does not dispute the biological data presented in the specification. However, the biological data presented merely associates HBM and Zmax1with

lipid levels. The teachings of Ye (see above) disputes the argument that the presented biological data substantially supports the asserted utility for the claimed methods.

The appellants argue that methods of identifying molecules that bind to a protein involved in lipid regulation have a well established utility (see p. 11, last paragraph). It is respectfully pointed out that the mere binding of a molecule to a protein involved in lipid regulation does not establish that the molecule itself is involved in lipid regulation, it only indicates that the molecule binds to the protein. It is possible that the molecule binds to the protein without a biological effect. The instant claims are drawn to methods of identifying molecules that are involved in lipid regulation by identifying molecules that bind to HBM and/or Zmax1 (as well as the nucleic acids encoding HBM and/or Zmax1). Therefore, in order for the instant claims to have substantial utility as a method for identifying molecules involved in lipid regulation, it must be established that HBM and Zmax1 are directly involved in lipid regulation. Appellants have presented data that indicates HBM and Zmax1 are highly homologous to the LDL receptor. Data is also presented in the specification that indicates HBM is associated with altered lipid levels. However, in view of the teachings of Willnow and Ye (discussed above) the data does not establish that HBM and Zmax1 are actually involved in lipid regulation. Therefore the instant methods are not supported by a substantial asserted utility.

With respect to the rejection of claims under 35 U.S.C § 112, first paragraph, the Appellants contend that the Office has not provided an analysis of the factors that is required to support such an assertion.

In reply, it is respectfully pointed out that that the utility rejection of record essentially contains an analysis of the factors that is required to support a rejection under 35 U.S.C § 112, first paragraph. Specifically, the factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

As indicated in the rejection of record, the claims are drawn to biological assays to identify molecules that are involved in lipid regulation wherein the assays comprise identifying molecules that bind to HBM and/or Zmax1, and identifying molecules that bind to the nucleic acids encoding HBM and/or Zmax1 (nature of the invention). The molecules can be a molecules such as a nucleic acid, protein, small molecule, etc. (breadth of the claims). The specification has disclosed that HBM is a polymorphism of Zmax1, that HBM has been associated with an altered lipid level, that Zmax1 and HBM have high sequence homology to the LDL receptor, and that several proteins, including ApoE bind to Zmax1 (Working examples and direction and guidance presented). However, the prior art (e.g., Ye et al.) indicates that lipid regulation is a complex multi-factorial process that involves many different factors, including diet as well as several different genes, and LDL receptors are a family of receptors that may be involved in lipid regulation, but may also have functions that are not related to lipid regulation (e.g., Willnow et al.). In view of the totality of the prior art, it is clear that a mere observation that HBM and Zmax1 are associated with lipid regulation and that they are members of the LDL receptor

family of proteins is not sufficient to establish that HBM and Zmax1 are directly involved in lipid regulation, which is required in order for the claimed methods to have utility and to be fully enabled (state of the prior art). No guidance has been shown by the specification as filed or based on the teachings of the prior art that HBM and Zmax1 are directly involved in lipid regulation. Therefore, additional experimentation would be required in order to first establish that HBM and Zmax1 are actually involved in lipid regulation (quantity of experimentation necessary in view of the level of guidance provided in the specification). Furthermore, the level of skill is deemed to be high since the methods are biological assays which are typically performed by individuals with advanced training in biology.

Therefore, an analysis of the factors required to support a rejection under 35 U.S.C § 112, first paragraph has been set forth in the rejection of record, and is the basis for the rejection of record.

The instant claims are drawn to methods of identifying molecules involved in lipid regulation wherein the methods comprise identifying molecules that bind to HBM and/or Zmax1, as well as identifying molecules that bind to the nucleic acid sequences that encode HBM and/or Zmax1. Since the claims are methods to identify molecules that are involved in lipid regulation, it is imperative that in order for the methods to have utility, all aspects of the claimed methods must utility in regulating lipid levels. Specifically, the methods comprise identifying molecules that bind to HBM and/or Zmax1 and molecules that bid to nucleic acids encoding HBM and/or Zmax1. Therefore, in order for the claimed method to have utility, HBM and Zmax1 must be involved in lipid regulation. It is noted that the prior art teaches that lipid regulation is a

complex multi-factorial process that involves many different elements including diet as well as several different genes/genetic polymorphisms. Furthermore, the prior art indicates that LDL receptors are a diverse family of proteins that include members that are involved in lipid regulation, as well as members which are not involved in lipid regulation. Therefore, considering the teaching of the prior art as a whole, the mere association of a protein or proteins with a particular lipid profile is not sufficient to establish that the protein(s) are directly involved in lipid regulation. An analysis of the data presented in the original specification and in the prior art reveals that at the time of filing HBM and Zmax1 were only associated with lipid regulation and there is insufficient evidence at the time of filing to establish that HBM and Zmax1 are directly involved in lipid regulation. Since the specification does not establish that HBM and Zmax1 are directly involved in lipid regulation, the claimed methods of identifying molecules that are involved in lipid regulation do not have substantial utility. Furthermore, since the claimed methods are not supported by a substantial utility, the claims are also not enabled.

Should the claimed methods be found to have substantial utility, the claims are not enabled because an undue amount of additional experimentation would be required in order for one of skill in the art to make and use the claimed methods to identify molecules involved in lipid regulation. In order for the method to actually identify molecules involved in lipid regulation, the genes used therein to screen with must be involved with lipid regulation. The specification has established that the HBM and Zmax1 genes are association with lipid regulation. However, a mere association between these genes and lipid regulation does not necessarily indicate that the genes have a causative effect on lipid regulation. Based on the lack of guidance in the specification, HBM and Zmax1 must be *de novo* characterized for their actual

biological function, and such characterization is considered to be undue. Thus the claimed methods are not enabled for screening for molecules involved in lipid regulation.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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